

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

(12) UK Patent Application (19) GB (11) 2 076 286 A

(21) Application No 8103106

(22) Date of filing
2 Feb 1981

(30) Priority data

(31) 8017078

169494

8023146

(32) 23 May 1980

15 Jul 1980

16 Jul 1980

(33) United Kingdom (GB)

United States of

America (US)

United Kingdom (GB)

(43) Application published
2 Dec 1981

(51) INT CL³ A61K 33/40

(52) Domestic classification

A5B 170 190 244 246

24X 24Y 26Y 272 27X

27Y 285 28Y 323 327

32Y 341 343 34Y 351

35Y 381 38Y 390 401

402 406 40Y 411 41Y

432 43Y 480 482 485

48Y 492 49Y 551 55Y

576 57Y 586 58Y 616

61Y 64X 64Y J M N

(56) Documents cited

GB 1539771

(58) Field of search

A5B

(71) Applicant

Quinoderm Limited

Manchester Road

Hollinwood

Oldham

Lancashire OL8 4PB

(72) Inventors

Harry Fitton

Bryan Westcott Fisher

(74) Agents

Sydney E M'Caw & Co


Saxone House

52-56 Market Street

Manchester M1 1PP

(54) Dermatological hydrogen peroxide compositions

(57) A dermatological composition in the form of a cream preparation comprises an oil medium dispersed in an aqueous medium, the aqueous medium containing hydrogen peroxide, and being buffered to a pH less than 7, and containing starch which has been gelled *in situ*.


102 (2) 103

W 0070/0700

SPECIFICATION

Dermatological compositions

- 5 This invention relates to dermatological compositions containing hydrogen peroxide. The invention is primarily concerned with such compositions for human therapeutic use. It is however to be understood that the invention is not intended to be limited to such use and thus for example compositions according to the invention may be used in a veterinary rather than a human context and/or may be of cosmetic rather than therapeutic effect. 5
- 10 Hydrogen peroxide has a well-known therapeutic and cosmetic effect in a dermatological context due to its ability to make available free oxygen in contact with the skin. Further, hydrogen peroxide is a readily available and relatively inexpensive substance which need only be used in small quantities for dermatological purposes due to the high proportion of available oxygen which it contains. In these respects therefore, hydrogen peroxide is a desirable 10
- 15 substance for dermatological use. Hydrogen peroxide has not however found wide acceptance in proprietary dermatological compositions due to certain disadvantages which arise with the use of the substance, in particular due to the fact that the substance is very unstable, due to the possible damage to skin tissue which may be caused if the skin is exposed to an unduly large amount of hydrogen peroxide, and due to the fact that hydrogen peroxide has a high surface 15
- 20 tension and therefore tends not to spread easily on the skin and make intimate contact therewith. 20
- An object of the present invention is to provide a dermatological composition containing hydrogen peroxide with which the above mentioned disadvantages can be avoided or at least appreciably reduced.
- 25 According to the invention therefore there is provided a dermatological composition in the form of a cream preparation which comprises an oil medium dispersed in an aqueous medium and incorporates starch gel, said aqueous medium containing hydrogen peroxide and a buffer to maintain the pH of the composition at less than 7, characterised in that the composition is formed by mixing starch with oil and water components and then converting the starch to a gel 30
- 30 *in situ* thereby to give a stable oil-in-water emulsion. 30
- In accordance with a preferred embodiment of the invention, the composition is an oil-in-water cream preparation of the 'vanishing' cream kind in which a small proportion of an oil medium is dispersed as an emulsion in a high proportion of an aqueous medium. Such cream preparation when applied to the skin does not have an oily or greasy feel and is therefore particularly 35
- 35 suitable for treating distressing skin conditions such as acne. 35
- With the composition of the invention, due to the incorporation of the hydrogen peroxide in an oil-in-water cream preparation and due to the presence of the acid buffer it had been found possible to achieve surprisingly good dermatological activity with a relatively small proportion of hydrogen peroxide (say no greater than 3.75% by weight) whereby the possibility of damage to 40
- 40 the skin tissue can be avoided or at least appreciably minimised, and also to achieve a remarkable stability to the extent that such dermatological activity can be expected to be retained after an appreciable period of storage. For good stability the nature and amount of buffer is preferably such as to give a pH range 2.5 to 6.5 and most preferably in the range 2.5 to 3.2. Further, the use of starch gel formed *in situ* has very important advantages with regard 45
- 45 to the incorporation of the hydrogen peroxide and also enables easy and intimate application to the skin. 45
- Thus, the starch gel, as formed *in situ*, becomes integrally incorporated in the oil-in-water emulsion and imparts properties thereto which facilitates the spreading of the composition over the surface of the skin despite the high surface tension of the hydrogen peroxide and which 50
- 50 facilitate ready 'vanishing' of such composition despite the presence of the oil medium. These properties arise, it is believed, because droplets of the oil medium are enclosed by the starch gel which acts effectively to combine the different components of the composition to give a stable uniform blend. 50
- A further important advantage arising from the use of the starch gel formed *in situ* is that the 55
- 55 hydrogen peroxide can be added at a final stage to a cold mixture of the other components. That is, oil components aqueous components and the starch can be mixed and treated, as by heating same, to produce the starch gel and it has been found that the resulting cream mixture when cold will readily incorporate hydrogen peroxide or indeed any other aqueous substance. Usually it is difficult to incorporate aqueous substances into cream mixtures without heating, 60
- 60 and of course hydrogen peroxide decomposes when heated. Thus, with the present invention, hydrogen peroxide can be readily incorporated in a stable composition without loss of activity. 60
- The starch used in forming the composition of the invention may be of any suitable origin, for example, it may be maize starch, rice starch, potato starch, wheat starch.
- The starch may be incorporated by adding same in the form of an aqueous slurry to a pre- 65
- 65 formed emulsion of the water and oil components, the resulting mixture then being heated and

stirred to form the gel. The emulsion may be pre-formed by adding the water component at a temperature of about 70°C (or higher) to the oil component also at a temperature of about 70°C (or higher) with stirring. The starch slurry may be added to such emulsion, the mixture then being further heated to 95–100°C with stirring and the resulting gel being allowed to cool with stirring.

The said oil component with which the starch is mixed prior to gel formation may comprise some or all of the total oil phase of the composition.

The oil medium may be of any suitable form appropriately selected such that it is dermatologically innocuous and such that it is compatible with the remaining constituents of the preparation. Thus, for example, the oil medium may comprise a saturated hydrogen wax and an emulsifying wax. The hydrocarbon wax may be one of more substances selected from hydrocarbons of general formula C_nH_{2n+2} and fatty acids of general formula $C_nH_{2n+1}COOH$ and may comprise for example hard paraffin wax, liquid paraffin Adeps Solidus, white or yellow soft paraffin wax. Preferably the substance known as "white soft paraffin wax" which is a semi-solid mixture of hydrocarbons obtained from petroleum and having a melting point in the range 38°C to 56°C is used. The emulsifying wax may be any suitable ionic or non-ionic substance. Thus for example it may be a non-ionic substance of general formula $R-CH_2-O(CH_2CH_2O)_nH$ and may be for example the substance known as Lanbritol Wax N21 (Trade Mark) which is a mixture of 86% by weight cetostearyl alcohol with 14% by weight of a non-ionic emulsifier. The cetostearyl alcohol contains 30% by weight cetyl alcohol and 70% by weight stearyl alcohol and the emulsifier is a cetyl-oleyl ether of polyethylene glycol having a mean chain length of 14 ethylene oxide units. Alternatively, the substance known as Cetomacrogol Emulsifying Wax BPC may be used. This substance comprises a compound having the formula $CH_3(CH_2)_m-O-CH_2(CH_2OCH_2)_nCH_2OH$ where m is 15 to 17 and n is 19 to 23, and four times its weight of cetostearyl alcohol. Alternatively, an anionic emulsifying wax may be used, such as Emulsifying Wax BPC, comprising 9 parts by weight cetostearyl alcohol and one part sodium lauryl sulphate or other sodium salt of a sulphated primary aliphatic alcohol or any mixture of salts.

With regard to the buffer, as mentioned this may be such as to maintain the pH at 2.5 to 6.5 and any suitable buffer may be used for this purpose. Thus, for example, there may be used an acid such as lactic acid, citric acid, tartaric acid, maleic acid, hydrosuccinic acid with an acid salt. Said acid salt may be any of sodium and potassium acid phosphate, sodium and potassium acid citrate, sodium and potassium acid tartrate.

In addition, if desired the composition may incorporate one or more of: a chelating agent, a pharmaceutically active quinoline derivative, chlorhexidine gluconate, urea, hydrocortisone, a corticosteroid, and other substances which provide an auxiliary therapeutic or cosmetic effect or act to improve (possibly synergistically) the therapeutic or cosmetic effect of one or more of the other constituents.

With regard to the quinoline derivative, the composition may incorporate such a derivative which is a bactericidal and keratolytic agent for example a substance selected from potassium 8-hydroxyquinoline sulphate, 8-hydroxyquinoline sulphate, iodochlorhydroxyquinoline, di-iodohydroxyquinoline and di(8-hydroxy-7-iodoquinoline-5-sulphonate).

With regard to the chelating agent, this may be provided for the purpose of minimising any loss of activity and discolouration of the quinoline derivative, where such derivative is provided, and in order to minimise any loss of available oxygen from the peroxide particularly due to the presence of metal ions in the preparation. Such chelating agent may be any suitable substance for example ethylenediamine tetra-acetic acid (EDTA) or any of the disodium, trisodium, dipotassium, and tripotassium salts of EDTA.

The starch incorporated in the preparation of the invention provides therapeutic astringent properties.

The invention will now be described further by way of example only.

Example 1: A cream preparation is prepared by mixing the following constituents;—

White Soft Paraffin Wax	9.5%	by weight	
Emulsifying Wax (e.g. Lanbritol Wax N21)	7%	" "	
5 Chelating Agent (EDTA)	0.09%	" "	5
Sodium Acid Phosphate	0.5%	" "	
Lactic Acid	0.5%	" "	
100% Hydrogen Peroxide	1.5%	" "	
Potassium 8-Hydroxyquinoline Sulphate	0.5%	" "	
10 Maize Starch	5.25%	" "	10
Water	to 100%	" "	

The paraffin wax, emulsifying wax, EDTA and some of the water are introduced into the bowl of a Hobart mixer. The bowl is placed in a water bath and the contents are heated to 95°C and stirred for a period of time (say about 60 minutes). 15

The sodium acid phosphate is dissolved in water (at say 50–60°C) and the starch is blended in with stirring to give a smooth slurry. This slurry is added to the mixture in the Hobart bowl and the temperature is brought back up to 95°C with stirring until a gel is formed. The gel is allowed to cool to below 40°C with further stirring. 20

The lactic acid and the potassium 8-hydroxyquinoline sulphate are separately dissolved in water and added to the cooled gel. The hydrogen peroxide is then blended into the contents of the Hobart bowl with stirring to give uniform mixture. 20

The resulting preparation is a smooth oil-in-water 'vanishing' cream having pH 2.6. The cream can be stored in tubes or other containers which should be opaque or of limited transparency to avoid decomposition in sunlight. The cream can be applied easily and smoothly to the skin and has good dermatological activity for example in the treatment of acne whilst being cosmetically acceptable. The cream does not tend to cause damage to skin tissue or undue irritation and is stable and retains its activity even after long storage. Any decomposition of the hydrogen peroxide merely produces water and does not give rise to the formation of any possibly harmful decomposition products. 30

In order to demonstrate that the preparation has anti-bacterial activity subsequent to manufacture thereof and subsequent to storage of the preparation, the following test were performed on a four-month old sample of the preparation. 35

The cream was placed in wells on plates sown with different strains of different bacterial species. After incubation of 24–72 hours presence and sizes of inhibition zones were noted. The tests were performed on nutrient agar or brain heart infusion agar and also on blood agar which breaks down hydrogen peroxide and rapidly eliminates its anti-bacterial activity. 35

The results were as follows:— 40

45 Species	Proportion of Strains Inhibited	
	Nutrient Agar or Brain Heart Infusion Agar	Blood Agar
<i>Staph. aureus</i>	16/16	16/16
<i>Str. pyogenes</i>	6/6	6/6
<i>Ps. aeruginosa</i>	6/6	0/8
50 Coliform species	10/10	2/16
Diphtheroid species	8/8	8/8
<i>Propionobacterium acnei</i>	2/2	2/2
<i>Clostridium welchi</i>	2/2	2/2

The preparation gave wide zones of inhibition for all strains of all species tested using nutrient agar or brain heart infusion agar. Removal of hydrogen peroxide by the blood agar gave rise to elimination of anti-bacterial activity in respect of all *Pseudomonas aeruginosa* strains and most of the Coliform species strains. In the case of the other species anti-bacterial activity was retained, probably due to the presence of quinoline derivative, but the inhibition zones were reduced in size by about one-half to two-thirds. 60

It can be seen therefore that the preparation contains hydrogen peroxide having utilisable anti-bacterial activity despite the incorporation of the hydrogen peroxide into the cream preparation and despite the storage of the preparation. 65

In the Example given above, the proportion of white soft Paraffin Wax may be varied between 65

1% and 38%, a corresponding change being made in the proportion of water.

Additionally or alternatively, it is possible to vary the proportion of hydrogen peroxide within a range having a preferred upper limit of 3.75%. A preferred range, however, is 0.75 to 2%. The proportion of water is correspondingly-changed to allow for any variation.

5 Additionally or alternatively, it is possible to replace the quinoline derivative with 100% Chlorhexidine Gluconate, a range having an upper limit of 2% being preferred for this constituent and 0.5% being a particularly preferred proportion. The proportion of water is correspondingly changed to allow for any variation in this respect. 5

10 Additionally or alternatively, urea can be incorporated in the composition in any desired suitable proportion, provided that the proportion of white soft Paraffin Wax and emulsifying wax is less than the proportion of water in the formulation. 10

15 It will be noted that with the embodiment described above the hydrogen peroxide can be intimately incorporated in an emulsion in the cold. Incorporation in a warm mix presents problems due to the thermal instability of hydrogen peroxide. The incorporation into an emulsion of course facilitates spreading on the skin. 15

It is to be understood that a composition according to the invention need not incorporate an auxiliary therapeutic agent (such as the quinoline derivative) but may comprise essentially only the hydrogen peroxide, oil medium, water, starch, and buffer as can be seen from the following example.

20 *Example 2:* 20

A cream preparation is prepared by mixing the following constituents:—

White Soft Paraffin Wax BP	9.5%	by weight	
Emulsifying Wax (e.g. Emulgade F supplied by Henkel & Cie GmbH of Dusseldorf)	7.0%	" "	25
Sodium Acid Phosphate	0.5%	" "	
Lactic Acid BP	0.5%	" "	
Hydrogen Peroxide BP 100%	1.5%	" "	
30 Maize Starch BP	5.25%	" "	30
Water BP	to 100%		

The resulting preparation is a smooth, white oil-in-water vanishing cream having a pH in the range of 2.5 to 3.2 and having an actual hydrogen peroxide content in the range 1.35% to 1.65%. A batch of the preparation having a pH 2.66 at 25°C and containing 1.544% hydrogen peroxide was analysed at intervals over a period of six months and the following successive results were obtained for hydrogen peroxide content 35

1.454
1.425
40 1.422 40
1.376
1.398

The preparation was therefore found to have good stability.

The above-mentioned batch was applied to Standard Lawns of Bacteria and the following 45 zones of inhibition were obtained. 45

Bacteria	No. of Strains	Zone of Inhibition (mm)	
5 <i>Staph. aureus</i>	33	36.24 \pm 2.07	5
<i>Streptococcal species</i>			
Group A <i>Str. pyogenes</i>	14	37.25 \pm 3.94	
Other <i>Strep. species</i>			
10 (Gps. A,B,C,G and non-groupable)	26	35.5 \pm 3.07	10
Mixed Gram negative species (<i>E. coli</i> , <i>Proteus sp.</i> , <i>Klebsiella sp.</i>)	19	27.53 \pm 2.78	
15 <i>Pseudomonas aeruginosa</i>	9	26.55 \pm 2.24	15
<i>Clostridium welchi</i>	6	39.2 \pm 1.64	
Diphtheroid organism (including <i>Prop. acnei</i> and two anaerobic species)	12	26.1 \pm 8.5	20

It is of course to be understood that the invention is not intended to be restricted to the details of this example composition. Thus, for example, a composition according to the invention need not be used for the treatment of acne, it may be used for the treatment of burns or for the treatment of any other suitable human or animal skin condition or for any other suitable dermatological purpose.

Indeed, the composition of the invention is particularly suitable for treating Stasis Ulcer and other kinds of ulcers of the skin. Further, whilst reference is made herein to hydrogen peroxide proportions up to 3.75% by weight it is to be understood that the composition of the invention renders possible the stable and convenient incorporation of higher proportions up to 5% or higher.

CLAIMS

1. A dermatological composition in the form of a cream preparation which comprises an oil medium dispersed in an aqueous medium, said aqueous medium containing hydrogen peroxide and a buffer to maintain the pH of the composition at less than 7, characterised in that the composition also incorporates starch gelled *in situ*.
2. A composition according to claim 1, characterised in that it comprises up to 3.75% by weight hydrogen peroxide.
3. A composition according to claim 2, characterised in that it comprises 0.75% to 2% by weight hydrogen peroxide.
4. A composition according to any one of claims 1 to 3, characterised in that it has a pH of 2.5 to 6.5.
5. A composition according to any one of claims 1 to 4, characterised in that the oil medium comprises a saturated hydrocarbon wax and an emulsifying wax.
6. A composition according to any one of claims 1 to 5, characterised in that the buffer comprises any of lactic acid, citric acid, tartaric acid, maleic acid, hydroxysuccinic acid with an acid salt.
7. A composition according to claim 6, characterised in that the acid salt is any of sodium and potassium acid phosphate, sodium and potassium acid citrate, sodium and potassium acid tartrate.
8. A composition according to any one of claims 1 to 7, characterised in that it incorporates one or more of a chelating agent, a pharmaceutically active quinoline derivative, chlorhexidine gluconate, urea, hydrocortisone, a corticosteroid.
9. A composition according to claim 8, characterised in that it incorporates said quinoline derivative which is any of potassium 8-hydroxyquinoline sulphate, 8-hydroxyquinoline sulphate, iodochlorhydroxyquinoline, di-iodohydroxyquinoline and di(8-hydroxy-7-iodoquinoline-5-sulphonate).
10. A composition according to claim 8 or 9, characterised in that it incorporates said chelating agent which is any of ethylenediamine tetra-acetic acid and the disodium, trisodium, dipotassium and tripotassium salts of this acid.
11. A composition substantially as hereinbefore described in the Examples.
12. A method of forming a composition according to claim 1, wherein starch is added to a preformed emulsion of water and oil components, and the resulting mixture is heated so that the starch gels *in situ*.

13. A method according to claim 12, wherein the starch is added in the form of an aqueous slurry.
14. A method according to claim 12 or 13, wherein the said emulsion is preformed by adding the water component to the oil component at a temperature of 70°C or higher.
- 5 15. A method according to claim 13, wherein the emulsion is heated to 95–100°C after addition of the starch. 5
16. A method according to any one of claims 12 to 15, wherein the said oil component with which the starch is mixed prior to gel formation comprises only part of the total oil phase of the composition.
- 10 17. A method according to claim 12, substantially as hereinbefore described in the Examples. 10
18. A composition formed by the method of any one of claims 12 to 16.

Printed for Her Majesty's Stationery Office by Burgess & Son (Abingdon) Ltd.—1981.

Published at The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.